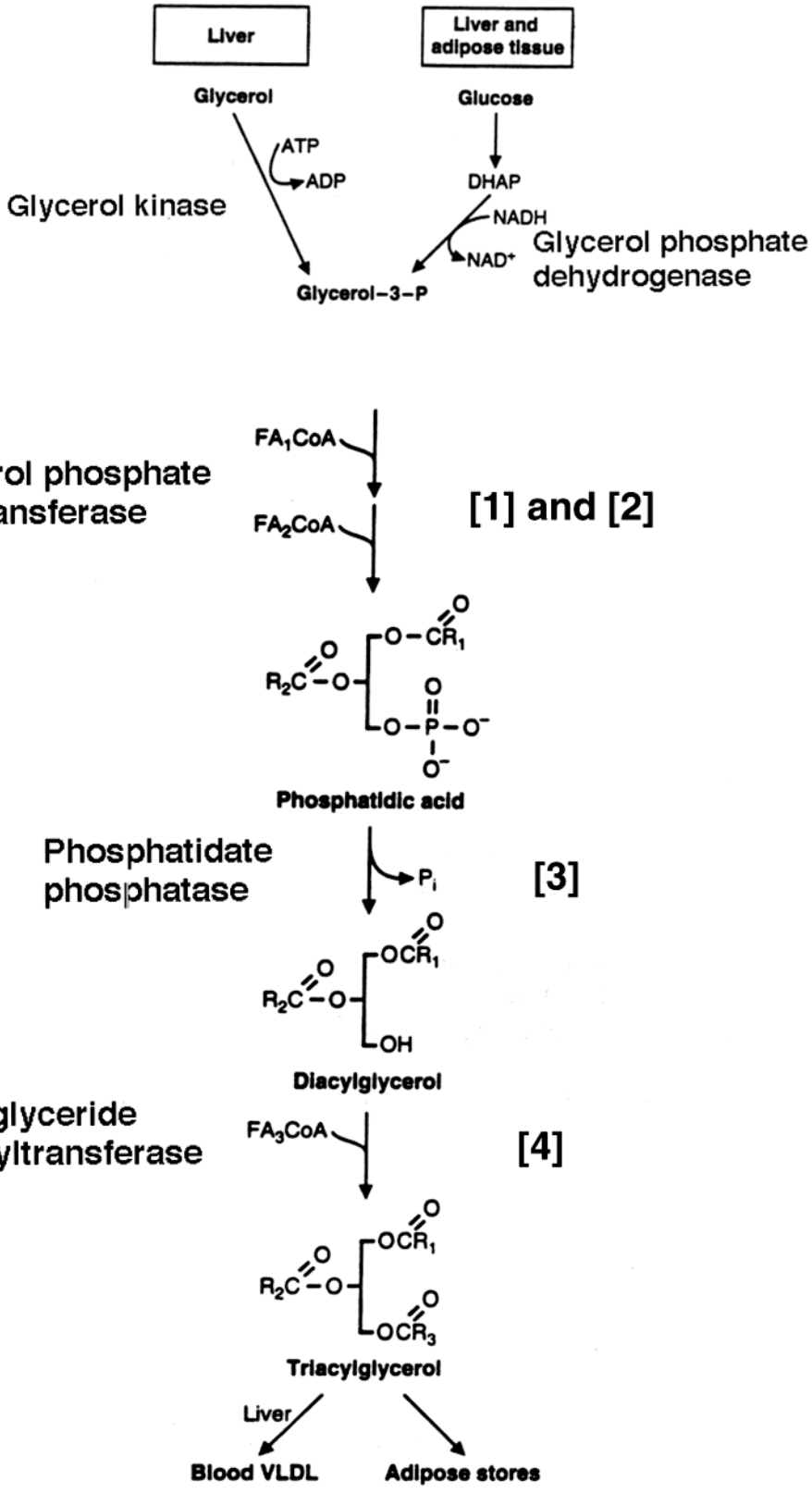
Lipoproteins I--6 Nov. 2002

1) Draw the biochemical steps in TG synthesis in the liver and adipose?


Liver
Liver and adipose tissue
Glycerol
Glucose
ATP
ADP
DHAP
Glycerol kinase
NADH
NAD+
Glycerol phosphate dehydrogenase
Glycerol-3-P
Glycerol phosphate acyltransferase
FA1CoA
FA2CoA
[1] and [2]
Phosphatidic acid
Phosphatidate phosphatase
Pi
[3]
Diacylglycerol
Diglyceride acyltransferase
FA3CoA
[4]
Triacylglycerol
Liver
Blood VLDL
Adipose stores

Where does glycerol 3-phosphate come from in the liver?
Both from glycolysis (interconversion of DHAP) and direct phosphorylation of glycerol by glycerol 3-kinase.

In adipose?

Only from DHAP produced in glycolysis.

What are the differences between TG synthesis in the liver and in intestinal epithelium?

In the 2-MG pathway that is used to synthesize TG in intestinal epithelium, TG is synthesized from fatty acids and 2-monoacylglycerol and not from glycerol 3-phosphate and fatty acids.

In the 2-MG pathway and in the liver (and adipose) pathway, the fatty acyl CoAs have to be activated before transfer. This is done by acyl CoA synthetase.

Because the synthesis occurs on the cytosolic face of the ER membrane with the hydrophobic portions of the intermediates partially embedded in the membrane, the acyl CoA synthetase that is used is probably the one associated with the ER membrane.

Once activated, the 2-MG pathway uses monoacylglycerol acyltransferase to produce diacylglycerol and release a free CoA. This step is unique to the 2-MG pathway.

Since the product does not contain a phosphoryl group at the 3-position, the next step in the 2-MG pathway is identical to the last step in the liver (and adipose) pathway, the transfer of a fatty acid to the three position of DG by diglyceride acyltransferase.

The fatty acid donor in this reaction is fatty acyl CoA and a molecule of CoA is released.

2) Where are VLDL, chylomicrons and HDL synthesized?

VLDL is synthesized in the liver, chylomicrons are synthesized in the intestinal epithelium and HDL is synthesized by BOTH tissues but the liver HDL is the major biosynthetic form.

What are the primary lipids and apoproteins associated with the secreted forms of each?

Nascent VLDL: 55% TG, 12% cholesterol esters in the hydrophobic core. This is surrounded by a monolayer of phospholipid that also contains unesterified cholesterol. VLDL contains Apo B-100 and small amounts of Apo C-II and Apo E. Additional amounts of Apo C-II and Apo E are acquired after secretion into the space of Disse (small lymphatic compartment) before metabolism by LPL.

Nascent chylomicrons: 88% TG, 3% cholesterol esters in the hydrophobic core. This is surrounded by a monolayer that contains phospholipid, unesterified cholesterol and resorbed bile acids. Chylomicrons contain Apo B-48, Apo A-I, and Apo A-II. This was simplified in lecture, but there actually are tiny amounts of Apo C-II and Apo E on the nascent form, but large amounts of Apo C-II and Apo E are rapidly acquired after secretion. Apo A-I and Apo A-II are rapidly exchanged off during chylo metabolism as well.

Nascent HDL: Two forms, lipid poor--**the major form**--(primarily just a secreted Apo A-I protein) and nascent discoidal HDL--**the minor form**. The lipid poor HDL is rapidly converted into nascent discoidal HDL by the action of ABCA1, a transporter of cholesterol and phospholipid. Lack of ABCA1 causes Tangier's disease. Nascent discoidal HDL is a disc of bilayer containing phospholipid and cholesterol surrounded by Apo A-I and Apo A-II. The Apo As contain stretches of sequence consisting of amphipathic alpha-helices. The hydrophobic portions of the helices contact the hydrophobic portions of the bilayer. Nascent discoidal HDL also contains Apo C-II, Apo D and Apo E and acquires LCAT from the palsma.

Are they directly secreted into the blood stream?

No

If not, how do they enter the blood stream?

VLDL and liver HDL are secreted into the space of Disse and enter the blood stream through discontinuities in the hepatic capillaries. The space of Disse can be thought of as a small specialized lymphatic space.

Chylomicrons and intestinal HDL are secreted into the lymph and enter the blood stream via the thoracic duct.

One thing I should emphasize is that the lipoprotein particles, especially chylomicrons, are so big that they cannot pass through the tight gap junctions that hold the capillary epithelium together. As a consequence of this, they cannot enter the blood stream directly and enter via the lymphatic system.

3) What are the primary functions of VLDL, chylomicrons and HDL in lipid transport in the blood stream?

VLDL is primarily involved in bringing endogenously synthesized TGs from the liver to the peripheral tissues for deposition (adipose) or energy production (muscle). VLDL also contains cholesterol esters (12%). Since VLDL is metabolized to LDL, both the cholesterol esters it contains that were synthesized by the liver and those that it acquired from HDL during metabolism (remember CETP) are present in LDL.

Chylomicrons are primarily involved in bringing exogenously acquired TGs from the gut to the peripheral tissues for deposition (adipose) or energy production (muscle). Some of the reabsorbed bile acids also ride back to the liver on chylomicros.

HDL is primarily involved in acquiring cholesterol from the peripheral tissues and bringing it back to the liver (reverse cholesterol transport using the SR-BI receptor to directly unload cholesterol esters or via indirect reverse cholesterol transport i.e. exchanging cholesterol esters for PC and TG of IDL during conversion to LDL and then LDL brings the cholesterol esters back to the liver).